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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/825,155 | 04/03/2001 | Ariel Ruiz i Altaba | 1049-1-008 N CON | 2618 |

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| EXAMINER | |
|---|---|
| NICKOL, GARY B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 19 |

DATE MAILED: 10/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/825,155 | ALTABA, ARIEL RUIZ I | |
| | Examiner | Art Unit | |
| | Gary B. Nickol Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Response to Amendment***

The Amendment filed February 12, 2003 (Paper No. 18) in response to the Office Action of November 12, 2002 is acknowledged and has been entered.

Claims 1-9 are pending.

Claims 1-8 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claim 9 is currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

***Petition to Correct Inventorship***

The petition to correct the inventorship of this application by including Nadia Dahmane as co-inventor was received on April 21, 2003. This petition has been carefully considered but is denied entry for the following reason:

The currently filed petition represents a *copy* of a previously filed petition submitted under 37 CFR 1.324 to correct the inventorship in US Patent No. 6,238,876. Applicants argue that the present petition to correct inventorship should be entered into the record because this continuation application (09/825,155) was filed on April 3, 2001 which was prior to the grant of the petition to correct inventorship. This argument has been considered but is not found

persuasive because the MPEP does not appear to support applicant's rationale for entering the petition. Further, a copy of a petition in a related allowed case does not provide definitive evidence that Ms. Dahmane is a co-inventor of the presently claimed invention because all statements attesting to her addition were made with regards to an independent and or distinct invention claimed in US Patent No. 6,238,876. Thus, a petition to correct inventorship in a patent application, other than a reissue application, pursuant to 35 U.S.C. 116, must be submitted under **37 CRF 1.48**.

**Objection re-visited:**

The previous office action (Paper No. 15, page 2) objected to the specification because there was no brief description of Figure 7. To the examiner, this figure appeared to show expression of Gli1, Gli3, Shh and S17 in BCC and SCC by RT-PCR which was supported by their issued Patent 6,238,876. Subsequently, Applicants amended the specification to insert such wording (Paper No. 18, page 2). However, the specification remains objected to because the figure itself is not labeled; there is only a "C" on the figure. Applicants should correct this by amending the figure to indicate that it is Figure 7.

**Rejection Maintained:**

Claim 9 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to predictably use the invention as claimed for the reasons of record and for the reasons set forth below.

Applicants argue (Paper No. 19, page 5) that a declaration submitted under 37 CFR 1.132 attests to protocols and compilation of data obtained from a series of experiments performed in the laboratory of the inventor which provide confirmatory evidence that small molecule inhibitors of Gli1, in particular, small interfering RNAs (siRNAS) inhibit proliferation of tumor cells. Applicants argue that these data support "the earlier studies provided in the instant application, whereby the inventor has provided evidence that Gli1 acts a target and mediator of Shh signaling, and that ectopic expression of Gli1 in the epidermal ectoderm of frog embryos results in tumor formation". These arguments and the declaration presented in Paper No.19 have been carefully considered but are not found persuasive. First, the data provided by Applicant's declaration is not commensurate in scope with the specification and claims as originally filed. For example, there is no guidance for one of skill in the art to predictably choose and use siRNA's in a pharmaceutical composition. Moreover, the disclosure fails to teach any particular structure or composition that would predictably function as a pharmaceutical composition for the intended purpose of treating a cellular debilitation, dysfunction, and or other disease state in mammals caused by the development and presence of sporadic basal cell carcinoma. Thus, it would appear that the newly presented data does not, in fact, support the earlier studies provided in the instant application. Secondly, the declaration argues that references provided (see Exhibit B) support the therapeutic use of siRNAs wherein applicants argue (Paper No. 18, page 5) that a skilled artisan would be cognizant of such references and as such would be fully able to practice the methods of the present invention. However, it is noted that all the references provided in

Exhibit B were post-filing date disclosures. In order to overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, *as filed*, would have enabled the claimed invention for one skilled in the art at the time of filing. As such, the earliest filing date of the as-filed application appears to be June 20, 1997. However, as evidenced by Fire *et al.* (US Patent No. 6,506,559, December 23, 1997), it would appear that the general use of siRNA's in-vitro was *not* well known to those of ordinary skill in the art, much less thought of as a pharmaceutical, until after applicant's date of priority. Furthermore, Caplen, N.J. (Trends in Biotech. Vol. 20. No.2, February 2002) teaches (page 50, 3rd column, 2nd paragraph) that the introduction of inhibitory RNAs is a "new" approach to the inhibition of gene expression and that it is probably too early to predict how widely RNAi will be used in vertebrate cells because it is unclear whether all mammalian cell types can support RNAi and work is still required to determine the key parameters that will generate consistent RNAi against any given RNA target. Thus, based on the current state of the art, it appears that the results presented in the declaration do not bear a reasonable correlation to what was well known to one of skill in the art at the time the invention was filed. Applicants are reminded that the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976).

To further substantiate the enablement of the claimed invention, applicants appear (Paper No. 18, page 6) to have correlated the experiments provided for in the Declaration with the

rationale outlined in MPEP 2107.03 which cites *Nelson v. Bowler* . However, it would appear that the issues regarding that particular passage of the MPEP do not parallel the current rejection because those issues relate to guidelines for examination of applications for compliance with the utility requirement. As there were no issues under 35 U.S.C. 101, applicant's arguments are not found persuasive. Applicants further point out that the issues of safety and tolerance of drugs under development for cancer therapy are relevant to the drug development process and the FDA, not to the immediate issues related to patentability of the present invention. However, with regards to the in vitro data presented in the declaration, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, in vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. Thus, it is maintained that that claim is not enabled because the specification fails to provide sufficient guidance and objective evidence to one skilled in the art to predictably use a pharmaceutical composition comprising a therapeutically effective amount of inhibitors of Gli1 (wherein said inhibitors are selected from the group consisting of small molecule antagonists of Gli1 expression and activity, ligands of Gli1, and agents that exhibit mimicry to Gli1) for the intended purpose of treating disease states in mammals caused by the development and presence of sporadic basal cell carcinoma. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

**New Rejections:**

Claim 9 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a pharmaceutical composition comprising a therapeutically effective amount of inhibitors of Gli1 (wherein said inhibitors are selected from the group consisting of small molecule antagonists of Gli1 expression and activity, ligands of Gli1, and agents that exhibit mimicry to Gli1).

However, the specification fails to provide sufficient guidance and or a description of molecules and or structures encompassed by the broad genus of inhibitors intended as pharmaceutical compositions. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). However, in the instant as filed application, there is no description of the

structure of these molecules nor is there any identifying information that would suggest to one of skill in the art that applicant was in possession of a particular inhibitory compound of Gli1.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As discussed above, since the skilled artisan cannot envision detailed chemical structures and or structures that would potentially inhibit Gli1, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

**All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol Ph.D.
Examiner
Art Unit 1642

GBN